**Inflammation mediates the deleterious effect of pancreatic ductal cells on human islet transplantation.**

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**Background and aims:** We have recently reported that pancreatic ductal cells have a negative impact on the metabolic evolution and grafted beta cell mass in experimental human islet transplantation. Ductal cells produce cytokines that may be detrimental to islet survival, but they also release angiogenic and growth factors that could improve islet survival and engraftment. The aim of this study was to investigate the mechanisms involved in the deleterious effect of pancreatic ductal cells on human islet transplantation.

**Material and methods:** Pancreases of cadaveric organ donors were processed for islet isolation and ductal cells were purified from the exocrine fraction. Pancreatic ductal cells clustered into pancreatospheres (DPS) after 3 day-culture in suspension. Human islets were cultured with/without DPS. Glucose-stimulated insulin secretion (GSIS) (ELISA), β-cell apoptosis (TUNEL) and gene expression (RT-qPCR) of inflammation mediators (*il-1β*, *il1ra*, *nlrp3*, *cxcl11*), macrophages (*cd68*, *cd206*), angiogenic factors (*vegfa*), hypoxia (*hif1a*) and growth factors (*igf2*) was determined after 48 hours in culture. Supernatants were collected after 24, 48 and 72 hours. Eight-hundred human islets (Tx Group) or 800 human islets + 600 DPS (Co-Tx Group) were transplanted under the kidney capsule of immunodeficient mice and gene expression was determined in grafts harvested on day 3 after transplantation.

**Results:** After 48 hours in culture, β-cell apoptosis was similar in islets cultured with/without DPS (Islets: 0.74 ± 0.31%; Islets + DPS: 0.66 ± 0.22%). GSIS was significantly reduced in islets cultured with DPS (stimulation index, Islets: 6.41 ± 1.14; Islets + DPS: 4.40 ± 0.54; $p<0.05$). *il-1β* and *cxcl11* gene expression was increased in islets cultured with DPS ($p<0.05$). IL-1β was detected in 12% and 40% of samples after 48 and 72 hours in culture respectively in islets + DPS preparations, whereas it was not detected at any time in islets cultured in the absence of DPS. *il1ra* expression was increased in islets cultured with DPS although the difference did not reach statistical significance. *igf2* expression was almost undetectable in DPS. Macrophage markers, as well as *nlrp3* and *vegfa* expression were similar in islets cultured with/without DPS. Grafts showed similar gene expression profiles than islets cultured with/without DPS. *il-1β* and *il1ra* expression was increased in Co-Tx grafts ($p<0.01$), while gene expression of macrophages, angiogenic factors, hypoxia and growth factors was similar in Tx and Co-Tx grafts.

**Conclusion:** Enrichment of human islet cell preparations with ductal cells has a negative impact on beta cell function. The inflammation induced by pancreatic ductal cells may mediate the deleterious effect of ductal cells on islet transplantation outcome.

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